A role for noncanonical microRNAs in the mammalian brain revealed by phenotypic differences in Dgcr8 versus Dicer1 knockouts and small RNA sequencing.

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Public Summary:
MicroRNAs are short RNA molecules that do not encode for proteins but rather regulate the production of proteins from messenger RNAs. Importantly, microRNAs have been implicated in a broad range of stem cell roles in both healthy and diseased tissues. MicroRNAs show great promise as both biomarkers and therapeutics for disease. Interesting, there is increasing evidence for other classes of short RNA molecules of potentially equal importance. Here, we uncover members of other classes of short RNAs and show for the first time their functional relevance by dissecting their roles in the mammalian brain. Interestingly, we also find that these brain short RNAs are rapidly evolving suggesting they may underlie some of the functional differences between mouse and human brains.

Scientific Abstract:
Noncanonical microRNAs (miRNAs) and endogenous small interfering RNAs (endo-siRNAs) are distinct subclasses of small RNAs that bypass the DGCR8/DROSHA Microprocessor but still require DICER1 for their biogenesis. What role, if any, they have in mammals remains unknown. To identify potential functional properties for these subclasses, we compared the phenotypes resulting from conditional deletion of Dgcr8 versus Dicer1 in post-mitotic neurons. The loss of Dicer1 resulted in an earlier lethality, more severe structural abnormalities, and increased apoptosis relative to that from Dgcr8 loss. Deep sequencing of small RNAs from the hippocampus and cortex of the conditional knockouts and control littermates identified multiple noncanonical microRNAs that were expressed at high levels in the brain relative to other tissues, including mirtrons and H/ACA snoRNA-derived small RNAs. In contrast, we found no evidence for endo-siRNAs in the brain. Taken together, our findings provide evidence for a diverse population of highly expressed noncanonical miRNAs that together are likely to play important functional roles in post-mitotic neurons.